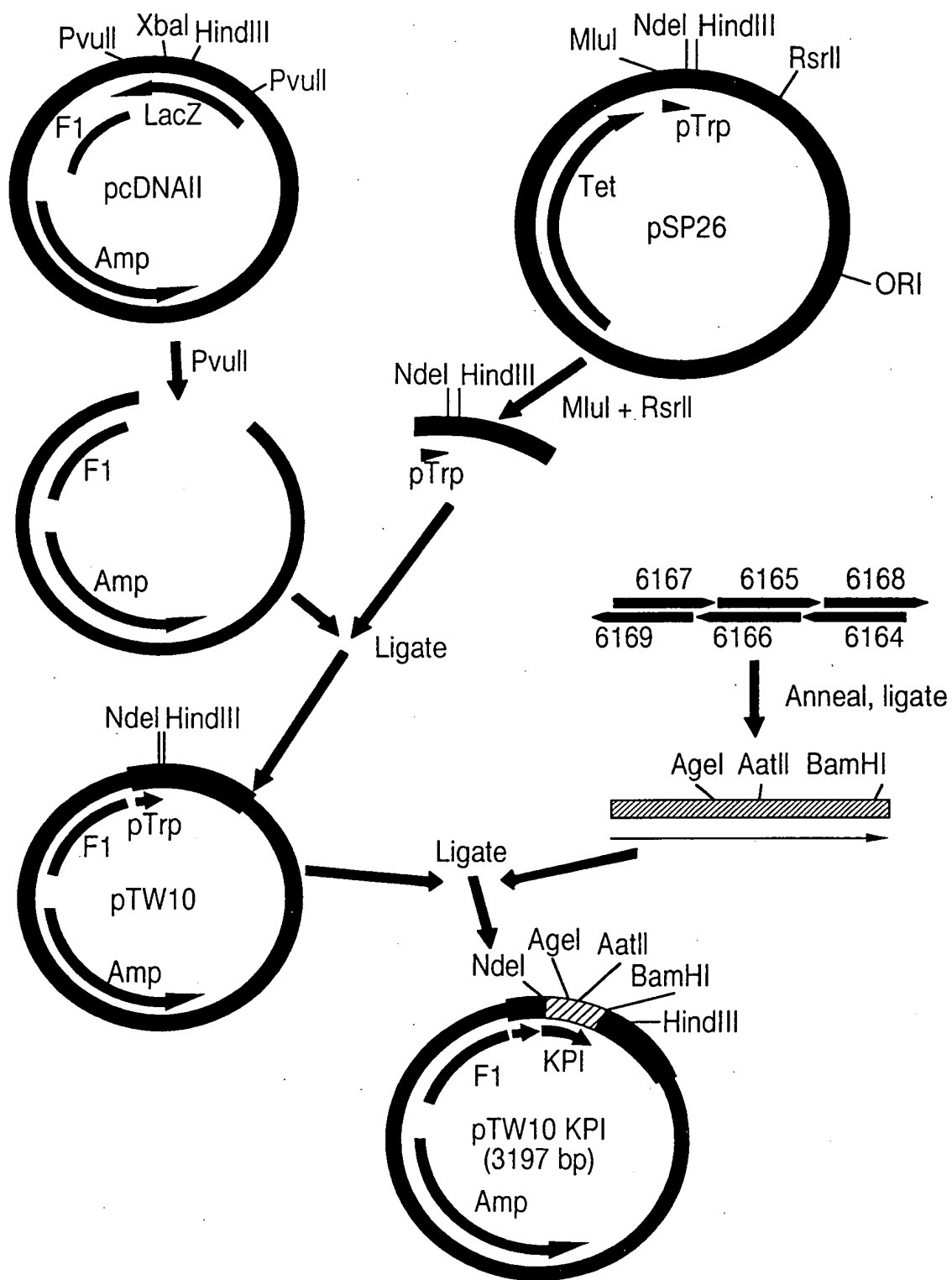


**FIG. 1**





Title: PROTEASE INHIBITOR  
PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 2

NdeI

TATG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCT GTG ACA AAA  
AC TTT GTT TCG TGA TAA CGT GAC CGT GAG AAT GGC AAT GAC AAA TGG GGA CAC TGT TTT  
▶ Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI

AgeI

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG  
CGG CTC CAC ACG AGA CTT GTT CGA CTC TGG CCA GGC ACG GCA CGT TAC TAG AGG GCG ACC  
▶ Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Met Ile Ser Arg Trp

AatII

TAC TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC AAC  
ATG AAA CTG CAG TGA CTT CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG  
▶ Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Tyr Gly Gly Cys Gly Gly Asn

BamHI

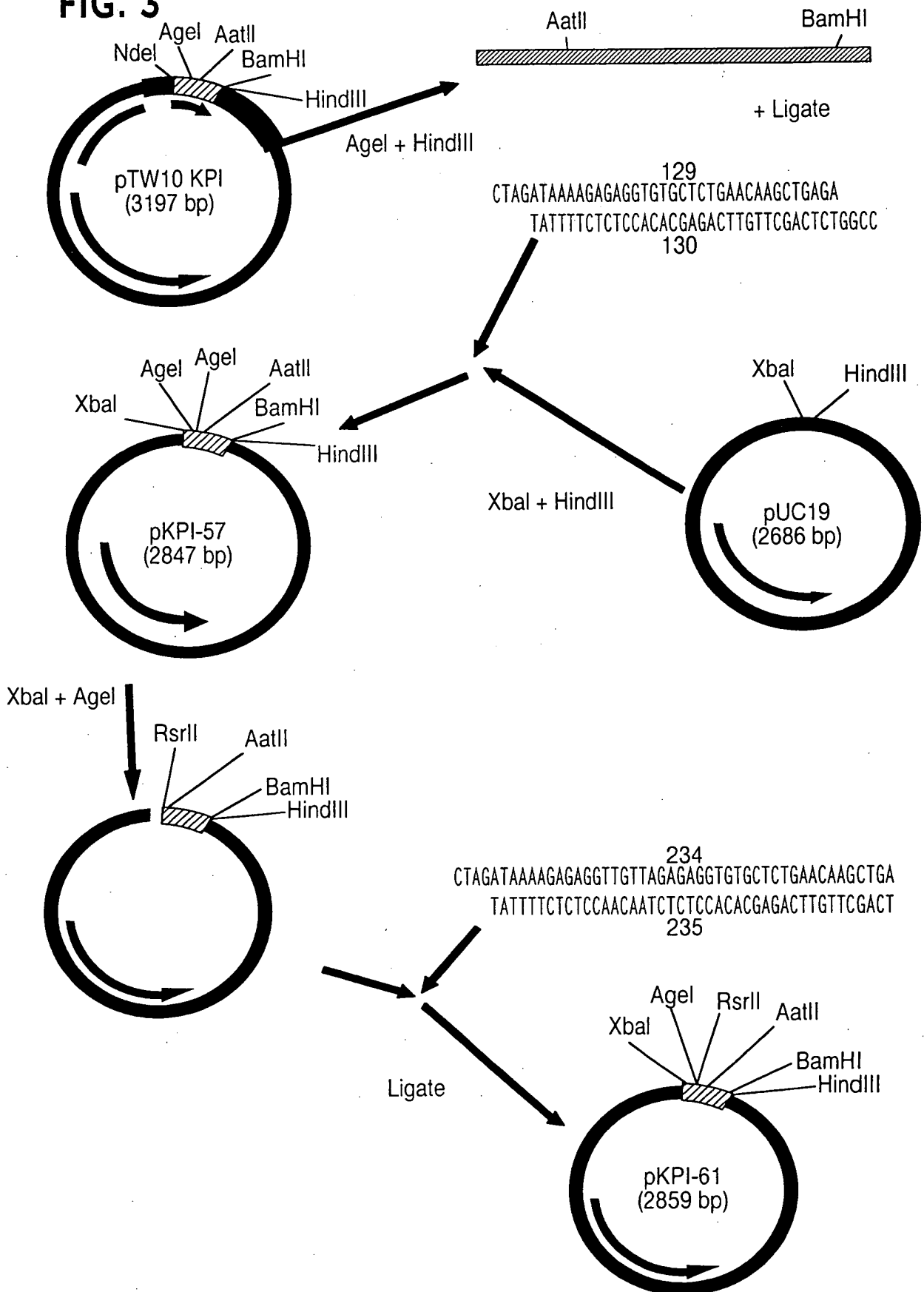
HindIII

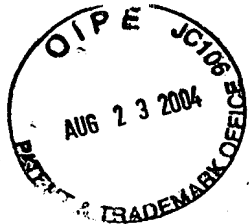
CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TA  
GCA TTG TTG AAA CTG TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA  
▶ Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



Title: PROTEASE INHIBITOR  
PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

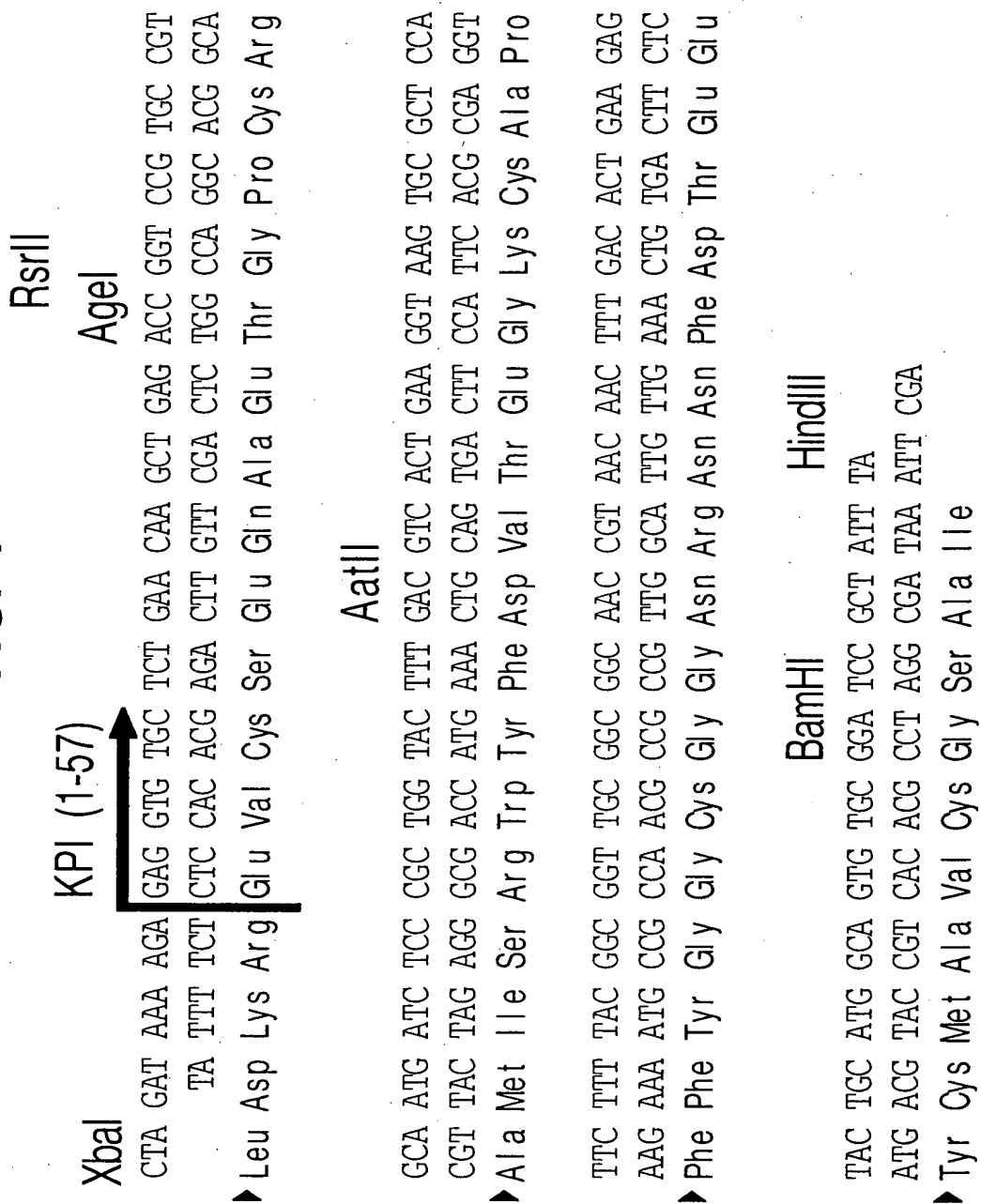
FIG. 3





Title: PROTEASE INHIBITOR  
PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

FIG. 4





Title: PROTEASE INHIBITOR  
PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

FIG. 5

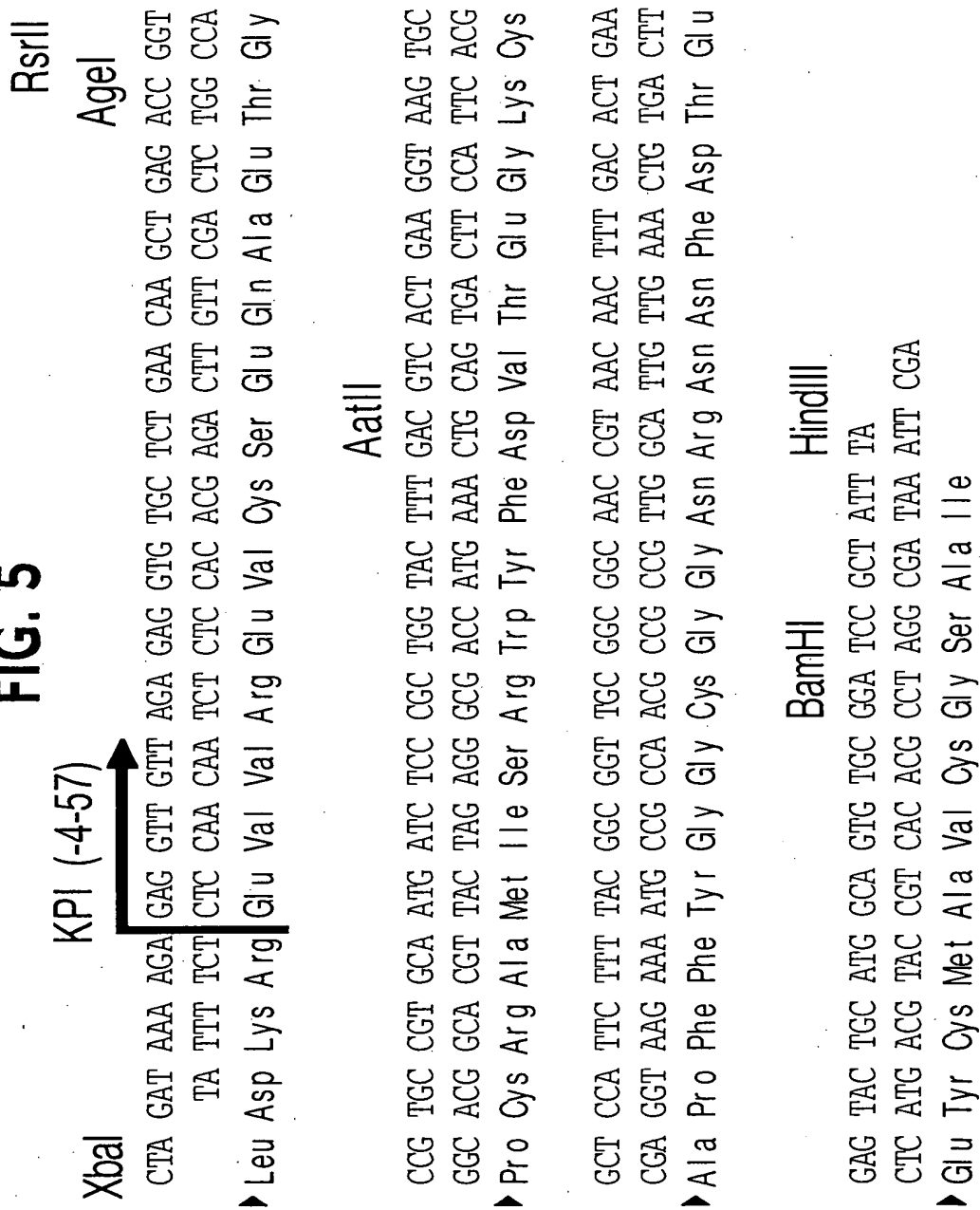
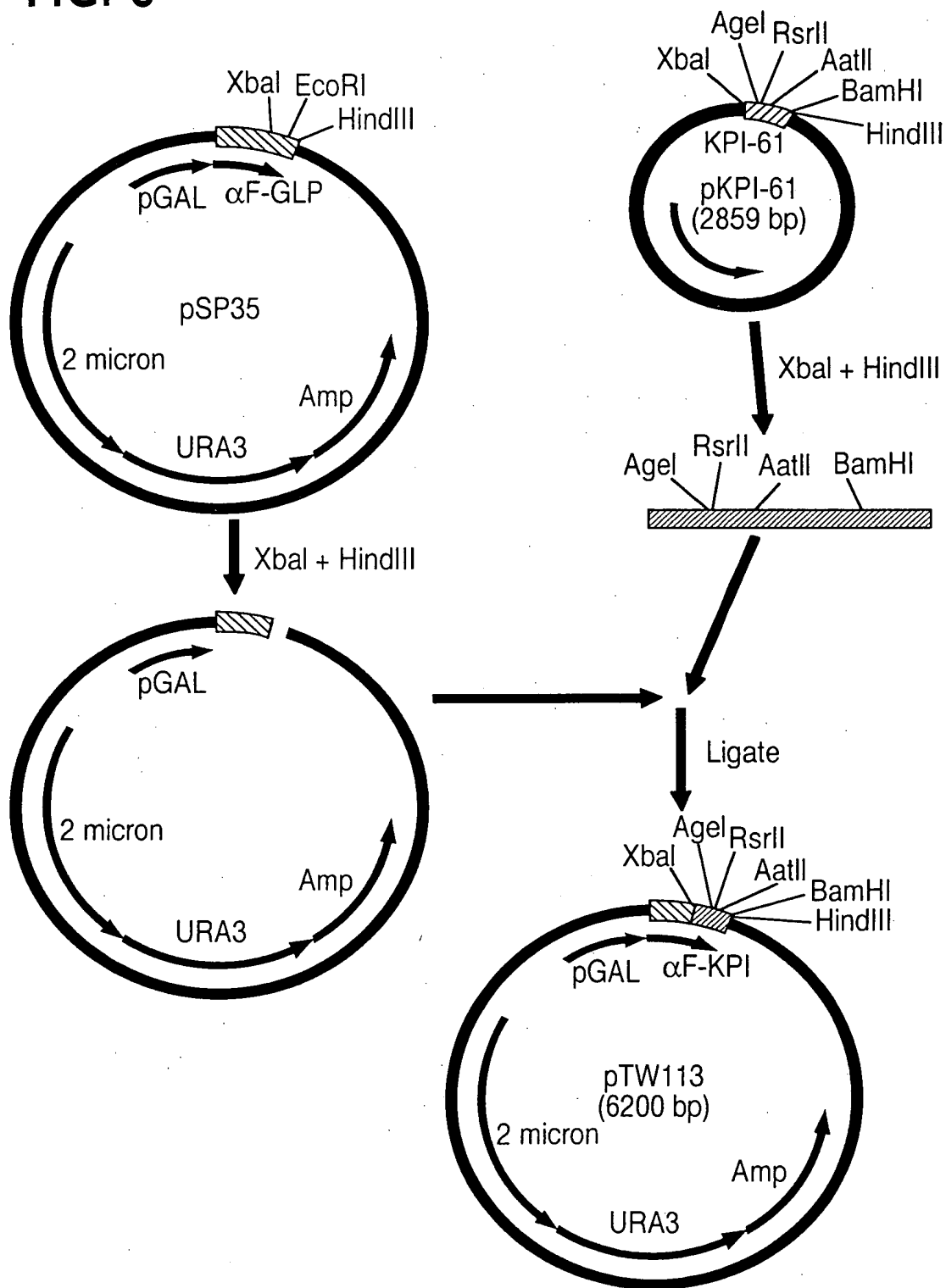


FIG. 6





Title: PROTEASE INHIBITOR  
PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

FIG. 7

$\alpha$ -factor

→

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57)

→

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

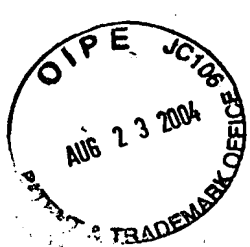
GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT TAC TAG AGG GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Met Ile Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



Title: PROTEASE INHIBITOR  
PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 8

KPI(-4-57)

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - Ile - Ser - Arg  
8 9 10 11 12 13 14 15 16 17 18

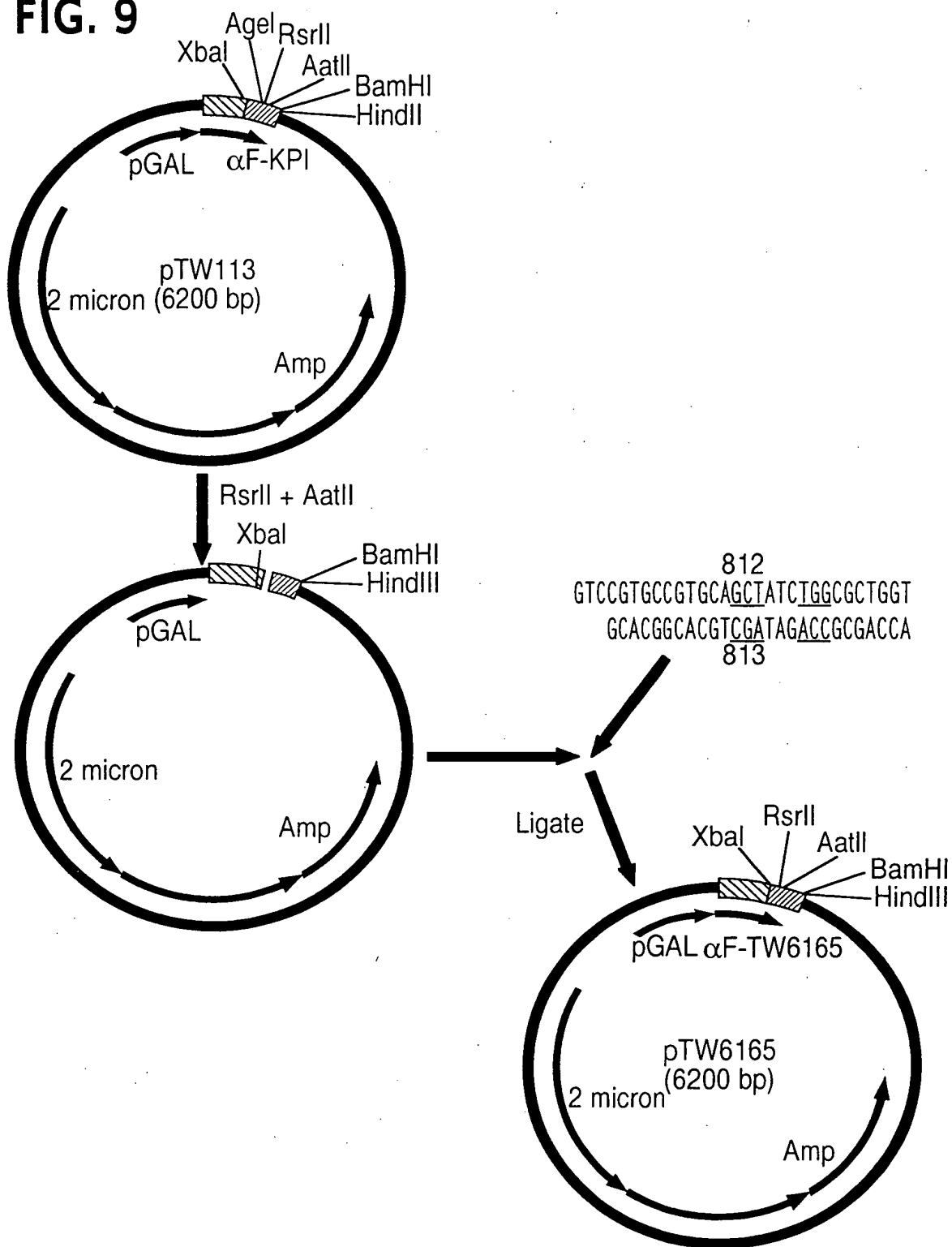
Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57

**FIG. 9**





## FIG. 10

pTW 6165

$\alpha$ -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15A, S17W)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TGG CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG ACC GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Trp Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



## FIG. 11

812	GTCCGTGCGGTGCAGCTATCTGGCGCTGGTACTTTGACGT GCACGGCAOGT <u>CGATAGAC</u> GGGACCATGAAAC	pTW6165 KPI(-4-57; M15A, S17F)
813		
814	GTCCGTGCGGTGCAGCTATCTACCGCTGGTACTTTGACGT GCACGGCAOGT <u>CGATAGAT</u> GGGACCATGAAAC	pTW6166 KPI(-4-57; M15A, S17Y)
815		
867	GTCCGTGCGGTGCATTGATCTTCCGCTGGTACTTTGACGT GCACGGCAOGT <u>AACTAGA</u> GGGACCATGAAAC	pTW6175 KPI(-4-57; M15L, S17F)
868		
1493	GTCCGTGCGGTGCATTGATCTACCGCTGGTACTTTGACGT GCACGGCAOGT <u>AACTAGAT</u> GGGACCATGAAAC	pBG028 KPI(-4-57; M15L, S17Y)
1494		
925	GTCCGTGCGGTGCAATGCACTTCCGCTGGTACTTTGACGT GCACGGCAOGTTAOGTGAAGGGGACCATGAAAC	pTW6183 KPI(-4-57; I16H, S17F)
926		
927	GTCCGTGCGGTGCAATGCACTACCGCTGGTACTTTGACGT GCACGGCAOGTTAOGTGATGGGACCATGAAAC	pTW6184 KPI(-4-57; I16H, S17Y)
928		
929	GTCCGTGCGGTGCAATGCACTGGCGCTGGTACTTTGACGT GCACGGCAOGTTAOGTGAAGGGGACCATGAAAC	pTW6185 KPI(-4-57; I16H, S17W)
930		
863	GTCCGTGCGGTGCAGCTCACTCCCGCTGGTACTTTGACGT GCACGGCAOGT <u>CGAGTGA</u> GGGACCATGAAAC	pTW6173 KPI(-4-57; M15A, I16H)
864		
865	GTCCGTGCGGTGCATTGCACTCCCGCTGGTACTTTGACGT GCACGGCAOGT <u>AAOGTGA</u> GGGACCATGAAAC	pTW6174 KPI(-4-57; M15L, I16H)
866		



## FIG. 12

pTW 6166

$\alpha$ -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15A, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TAC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



## FIG. 13

pTW 6175

$\alpha$ -factor

→  
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala  
  
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val  
  
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn  
  
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15L, S17F)

→  
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

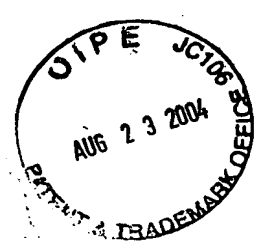
AatII

GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Leu Ile Phe Arg Trp Tyr Phe Asp Val Thr Glu  
  
GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



## FIG. 14

pBG028

$\alpha$ -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15L, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TAC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Leu Ile Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



## FIG. 15

pTW6183

$\alpha$ -factor

→  
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala  
  
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val  
  
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn  
  
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

KPI(-4-57; I16H, S17F)

XbaI

→  
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

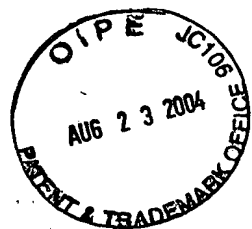
AatII

GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TTC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT TAC GTG AAG GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Met His Phe Arg Trp Tyr Phe Asp Val Thr Glu  
  
GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



pTW6184

## FIG. 16

$\alpha$ -factor

→  
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala  
  
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val  
  
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn  
  
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; I16H, S17Y)

→  
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TAC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT TAC GTG ATG GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Met His Tyr Arg Trp Tyr Phe Asp Val Thr Glu  
  
GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



pTW6185

## FIG. 17

$\alpha$ -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala  
  
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val  
  
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn  
  
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; I16H, S17W)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TGG CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT TAC GTG ACC GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Met His Trp Arg Trp Tyr Phe Asp Val Thr Glu  
  
GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



pTW6173

## FIG. 18

$\alpha$ -factor

→  
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala  
  
GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val  
  
ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn  
  
AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15A, I16H)

→  
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT CGA GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Ala His Ser Arg Trp Tyr Phe Asp Val Thr Glu  
  
GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



pTW6174

## FIG. 19

$\alpha$ -factor

→  
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA  
▶ Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG  
▶ Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG  
▶ Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT  
▶ Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15L, I16H)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT  
▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA TTG CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT AAC GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT  
▶ Ala Glu Thr Gly Pro Cys Arg Ala Leu His Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG  
▶ Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A  
▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



Title: PROTEASE INHIBITOR  
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Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 20

KPI(-4-57; M15A, S17W) TW6165

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

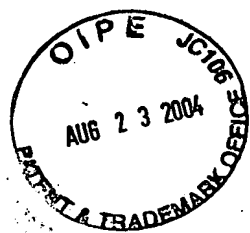
Glu - Thr - Gly - Pro - Cys - Arg - Ala - Ala - Ile - Trp - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



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Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 21

KPI(-4-57; M15A, S17Y) TW6166

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

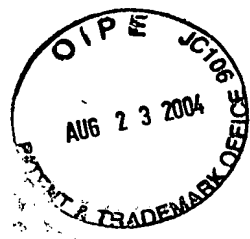
Glu - Thr - Gly - Pro - Cys - Arg - Ala - Ala - Ile - Tyr - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



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PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 22

KPI(-4-57; M15L, S17F) TW6175

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

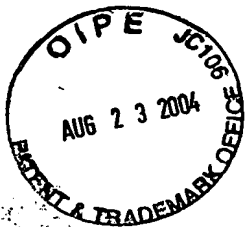
Glu - Thr - Gly - Pro - Cys - Arg - Ala - Leu - Ile - Phe - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



Title: PROTEASE INHIBITOR  
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Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 23

KPI(-4-57; M15L, S17Y) BG028

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

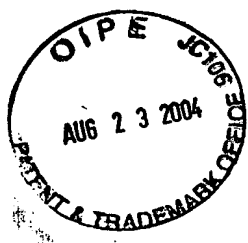
Glu - Thr - Gly - Pro - Cys - Arg - Ala - Leu - Ile - Tyr - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



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Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 24

KPI(-4-57; I16H, S17F) TW6183

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

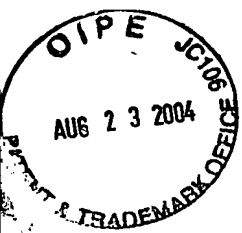
Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - His - Phe - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



Title: PROTEASE INHIBITOR  
PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 25

KPI(-4-57; I16H, S17Y) TW6184

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - His - Tyr - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



Title: PROTEASE INHIBITOR  
PEPTIDES  
Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 26

KPI(-4-57; I16H, S17W) TW6185

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

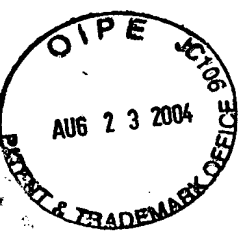
Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - His - Trp - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



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Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 27

KPI(-4-57; M15A, S17F) DD185

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

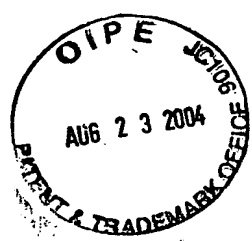
Glu - Thr - Gly - Pro - Cys - Arg - Ala - Ala - Ile - Phe - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



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Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 28

KPI(-4-57; M15A, I16H) TW6173

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala  
-4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Ala - His - SerTrp - Arg  
8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala  
19 20 21 22 23 24 25 26 27 28 29

Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg  
30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala  
41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile  
52 53 54 55 56 57



Title: PROTEASE INHIBITOR  
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Inventor(s): R. Tyler WHITE et al.  
Appl. No.: 10/076,604

## FIG. 29

KPI(-4-57; M15L, I16H) TW6174

Glu	- Val	- Val	- Arg	- Glu	- Val	- Cys	- Ser	- Glu	- Gln	- Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	- Thr	- Gly	- Pro	- Cys	- Arg	- Ala	- <u>Leu</u>	- <u>His</u>	- Ser	- Arg
8	9	10	11	12	13	14	15	16	17	18

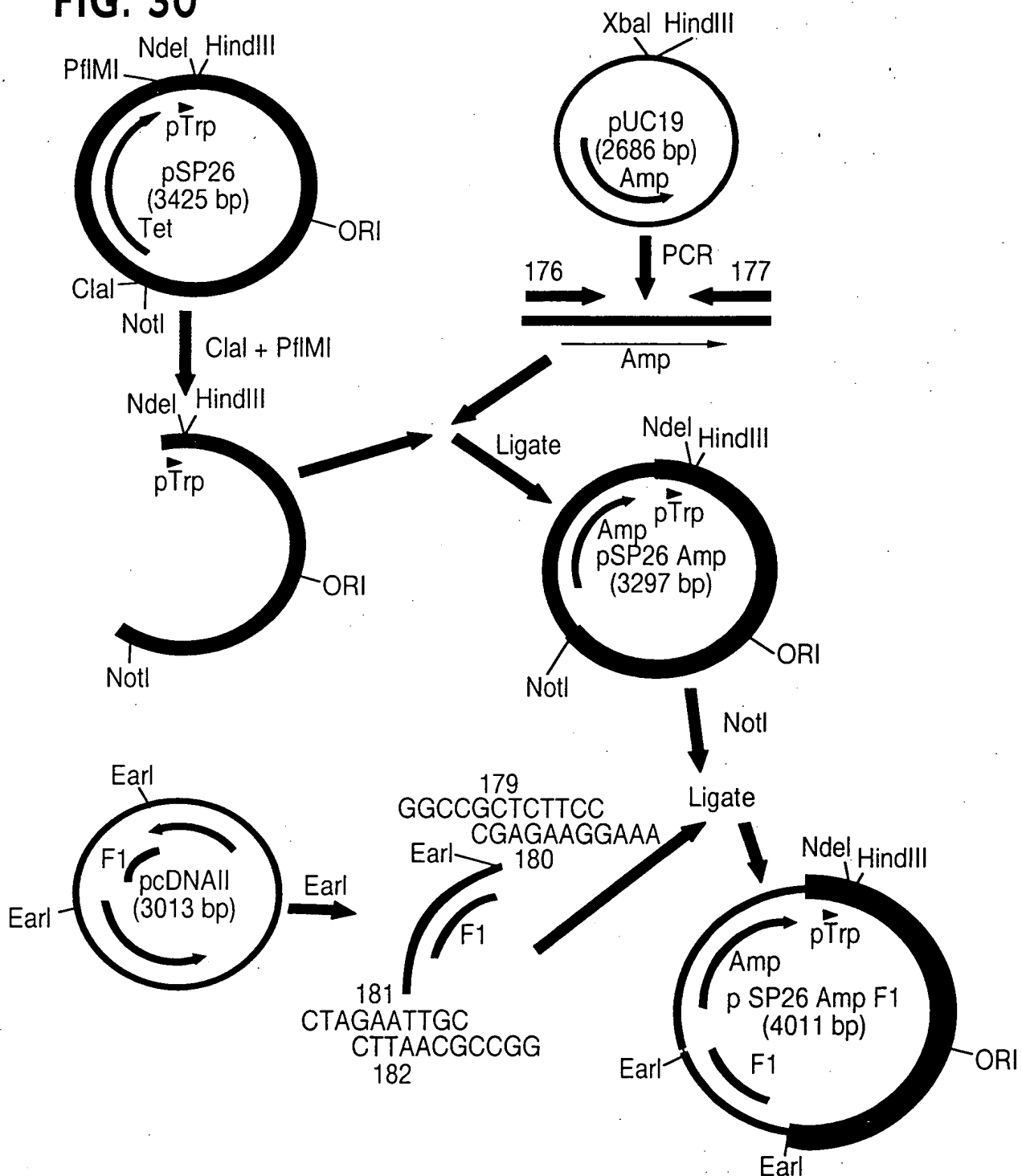
Trp	- Tyr	- Phe	- Asp	- Val	- Thr	- Glu	- Gly	- Lys	- Cys	- Ala
19	20	21	22	23	24	25	26	27	28	29

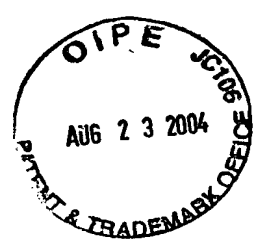
Pro	- Phe	- Phe	- Tyr	- Gly	- Gly	- Cys	- Gly	- Gly	- Asn	- Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	- Asn	- Phe	- Asp	- Thr	- Glu	- Glu	- Tyr	- Cys	- Met	- Ala
41	42	43	44	45	46	47	48	49	50	51

Val	- Cys	- Gly	- Ser	- Ala	- Ile
52	53	54	55	56	57

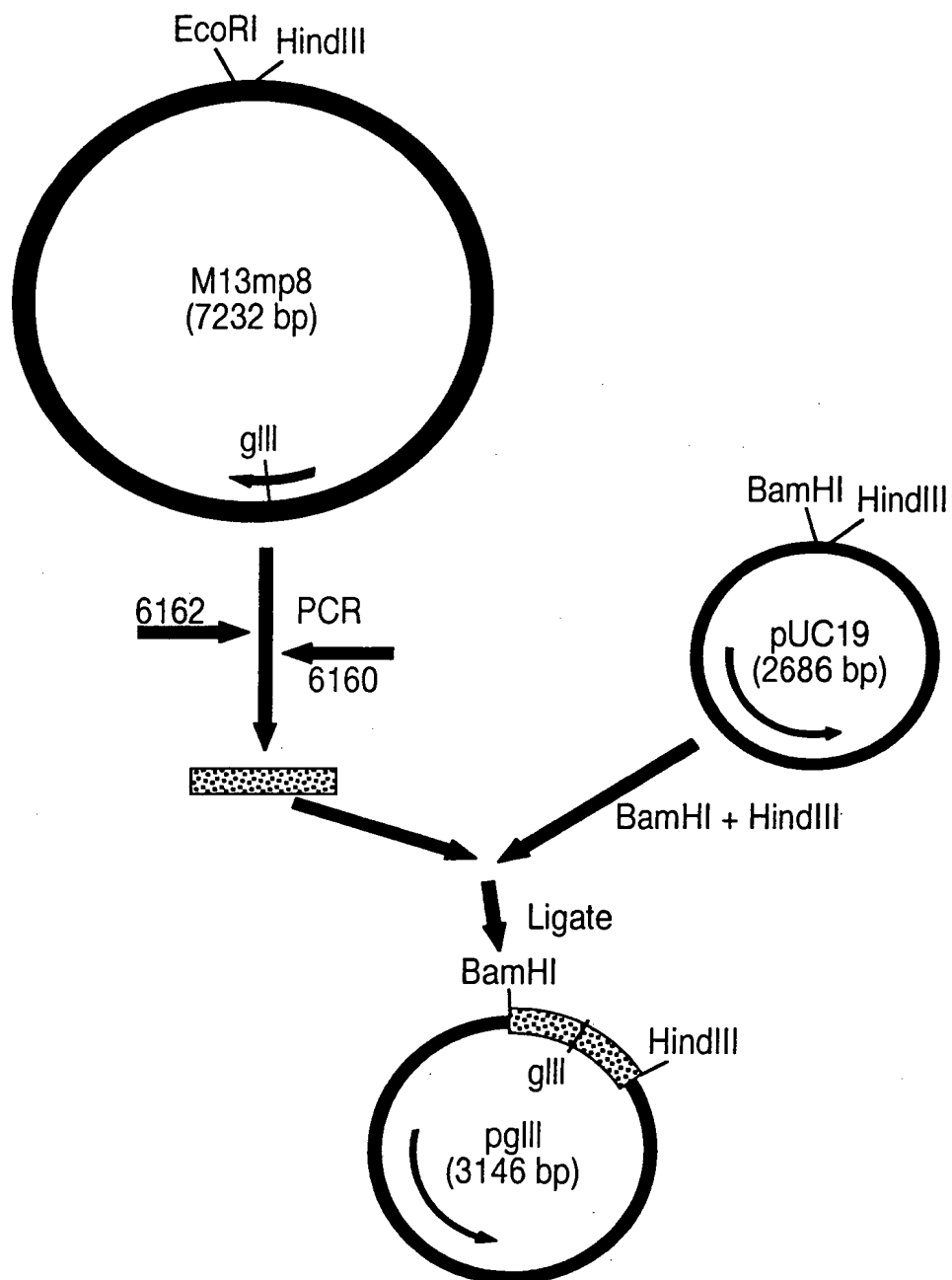
**FIG. 30**



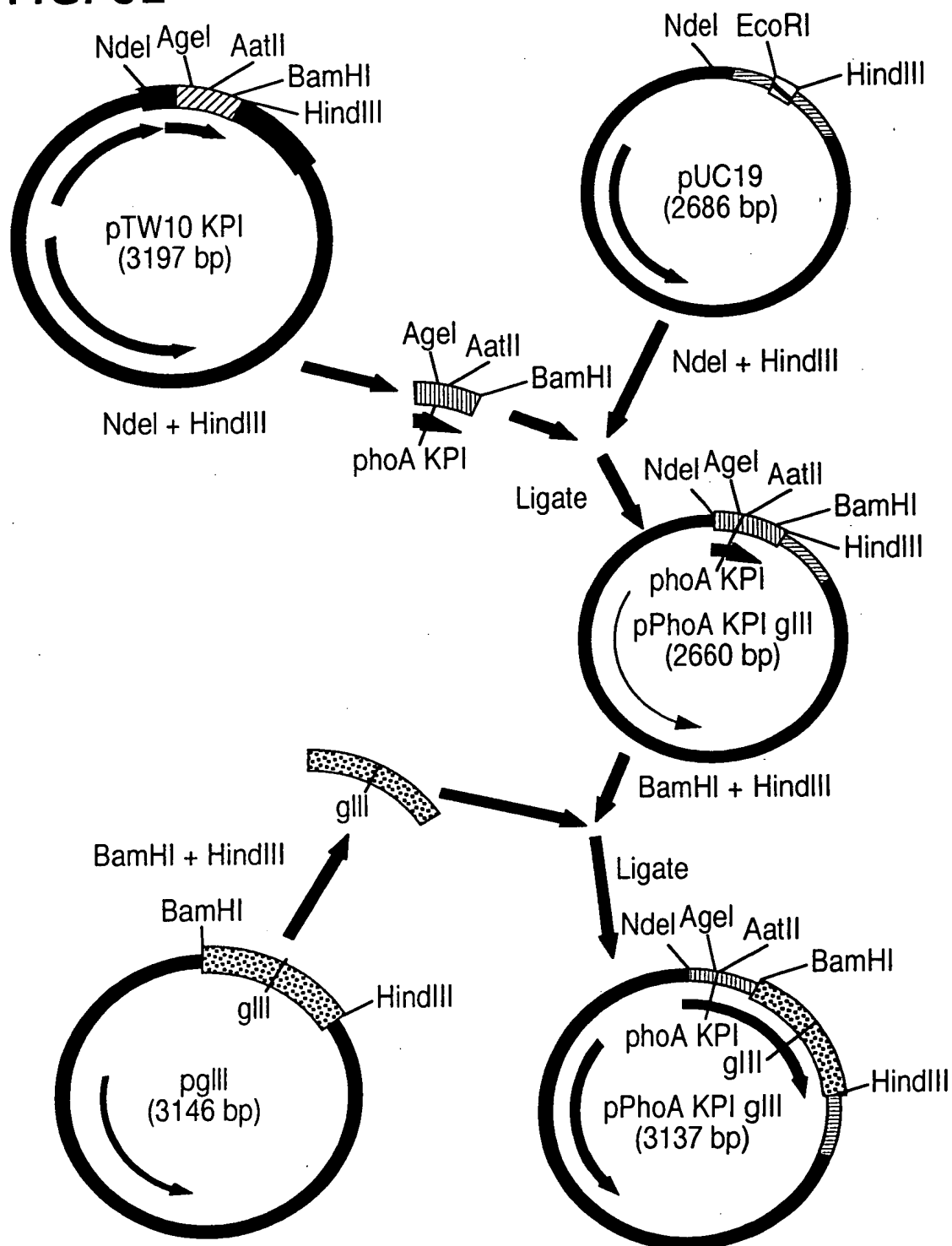


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Appl. No.: 10/076,604

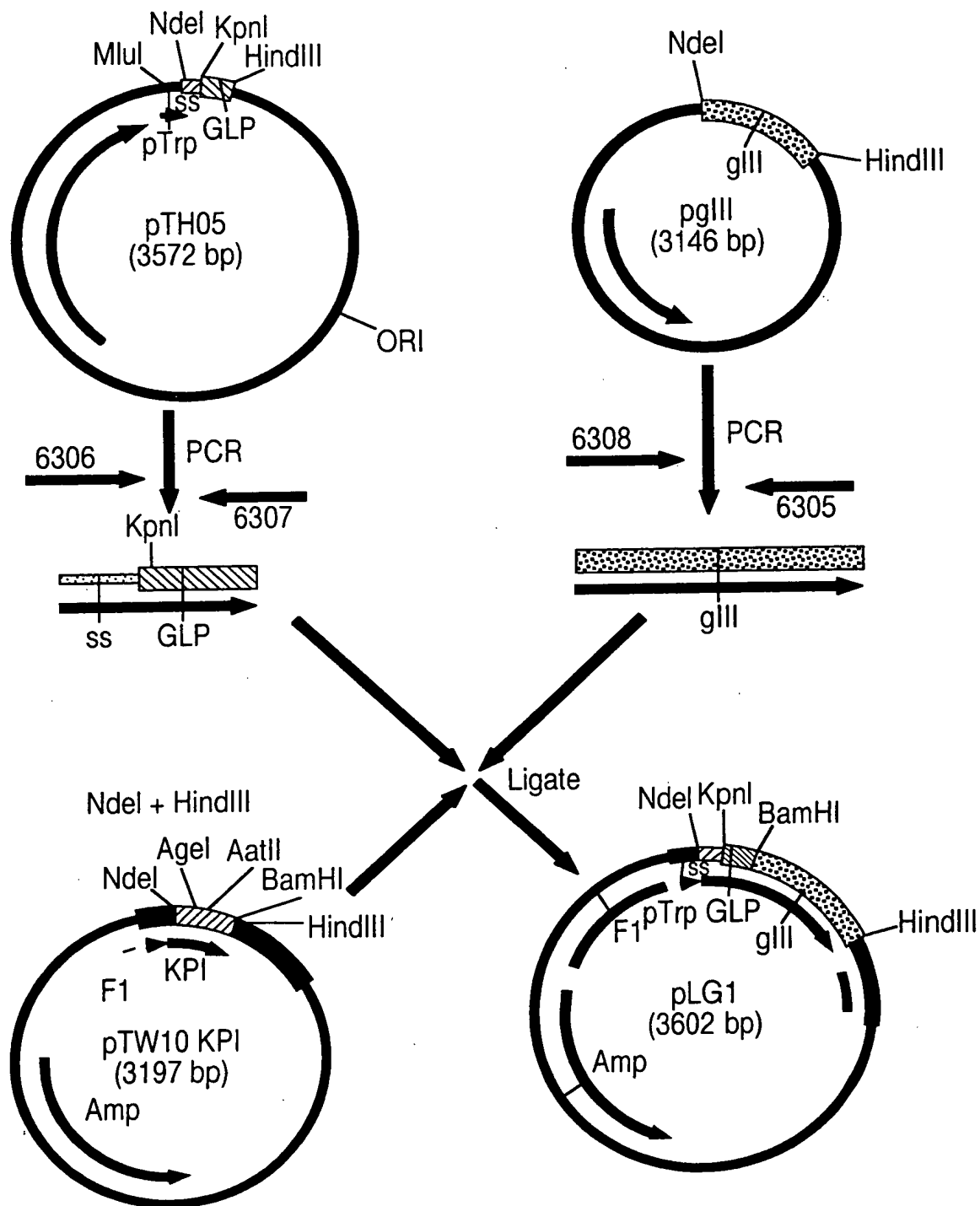
**FIG. 31**



**FIG. 32**



**FIG. 33**



**FIG. 34**

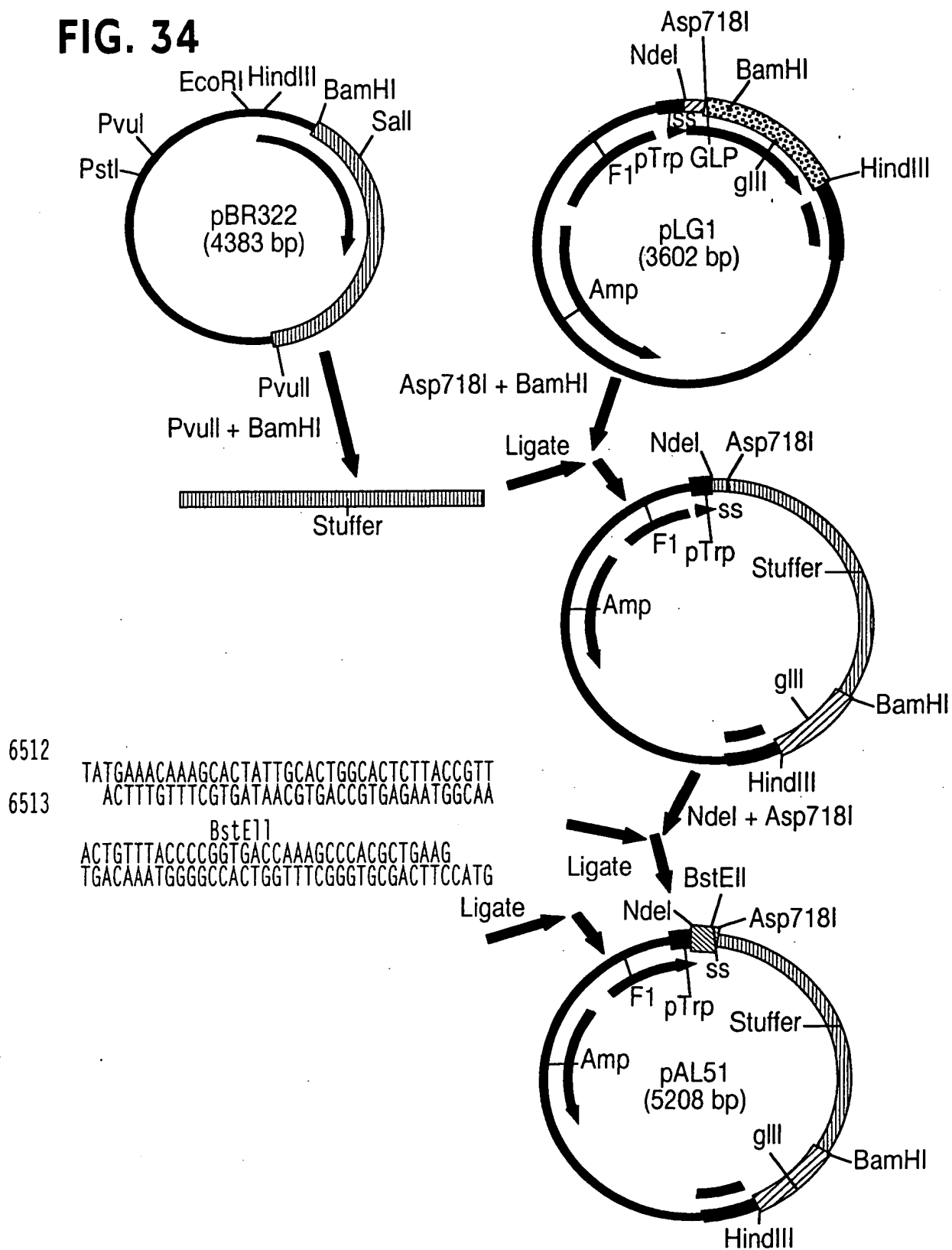
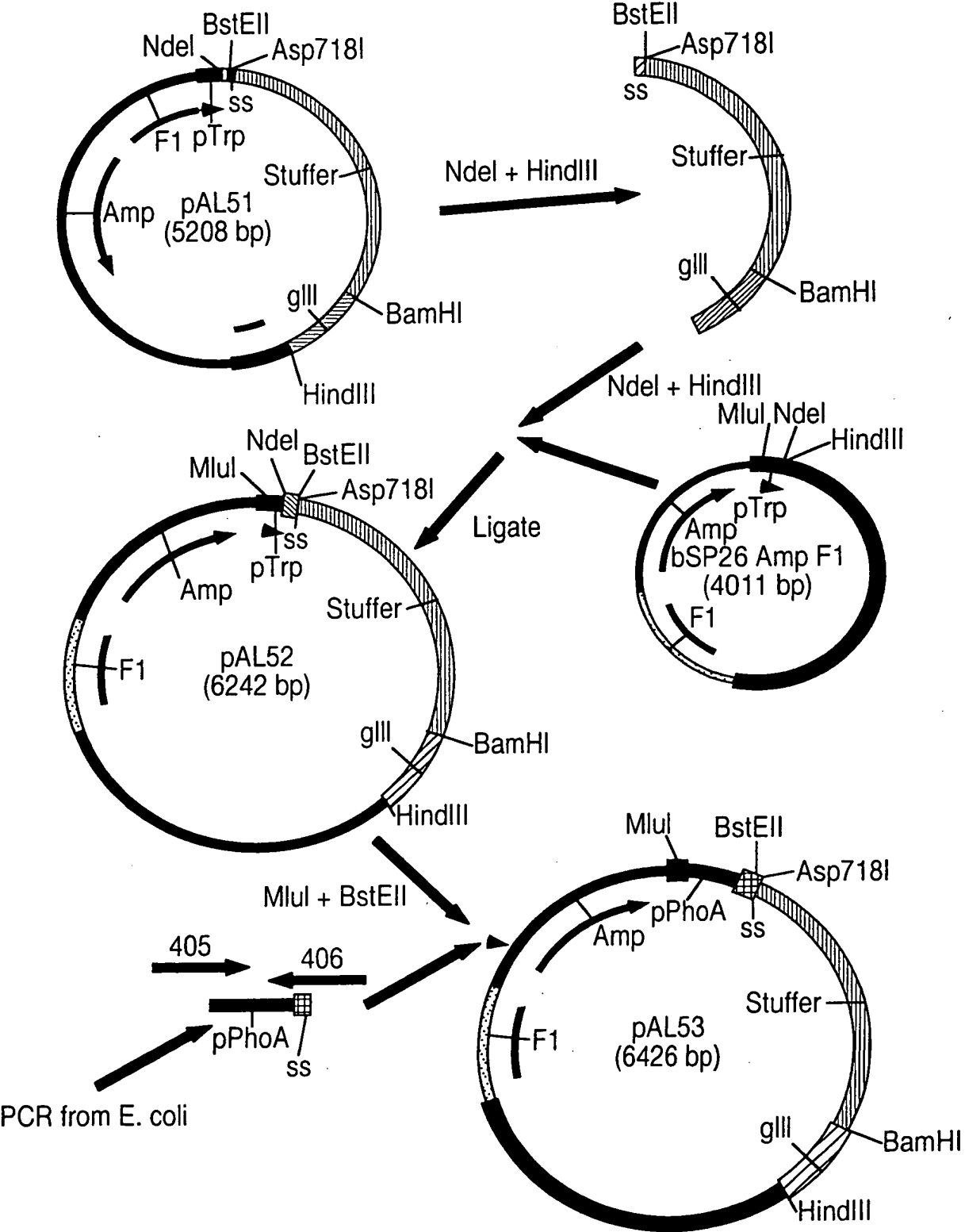
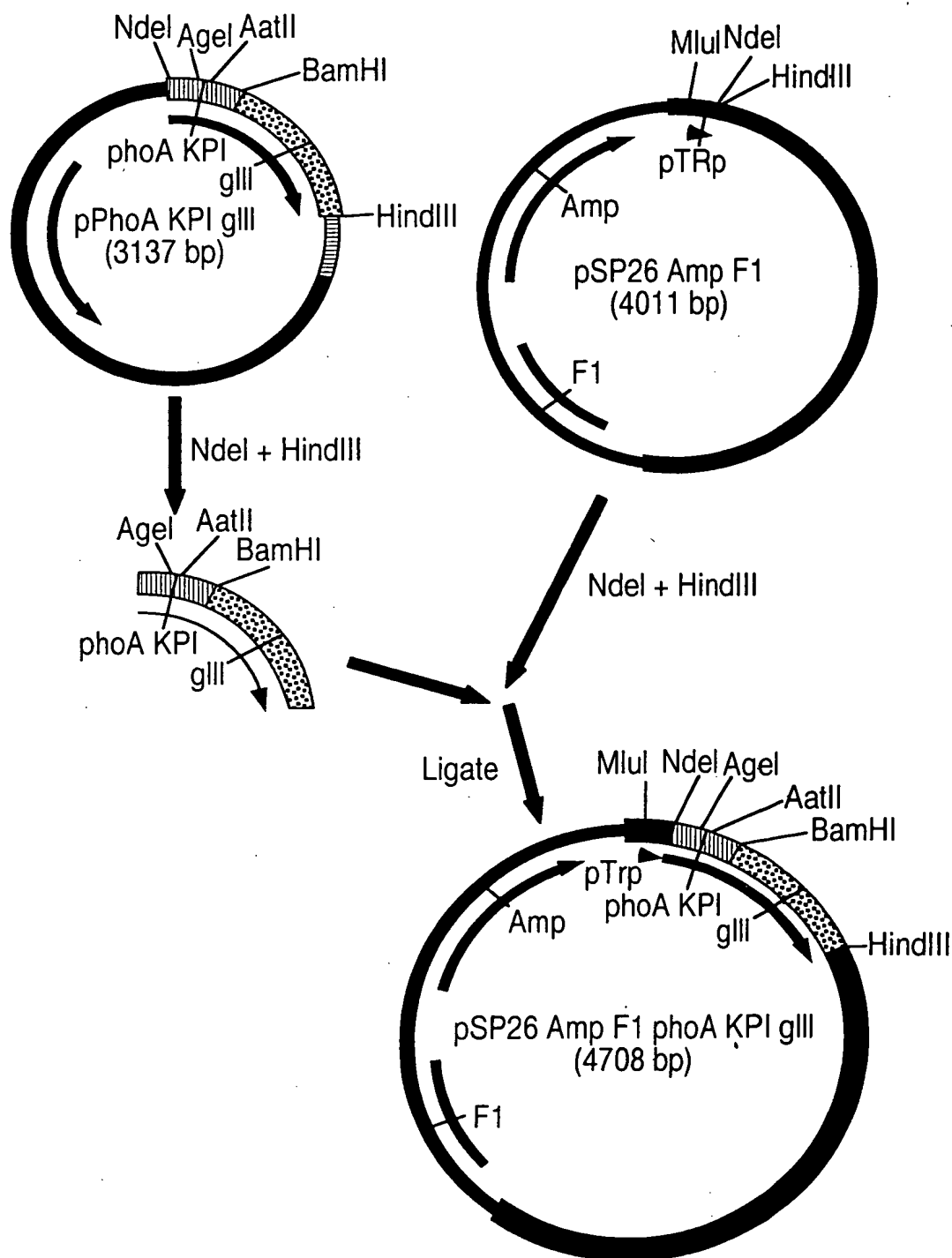




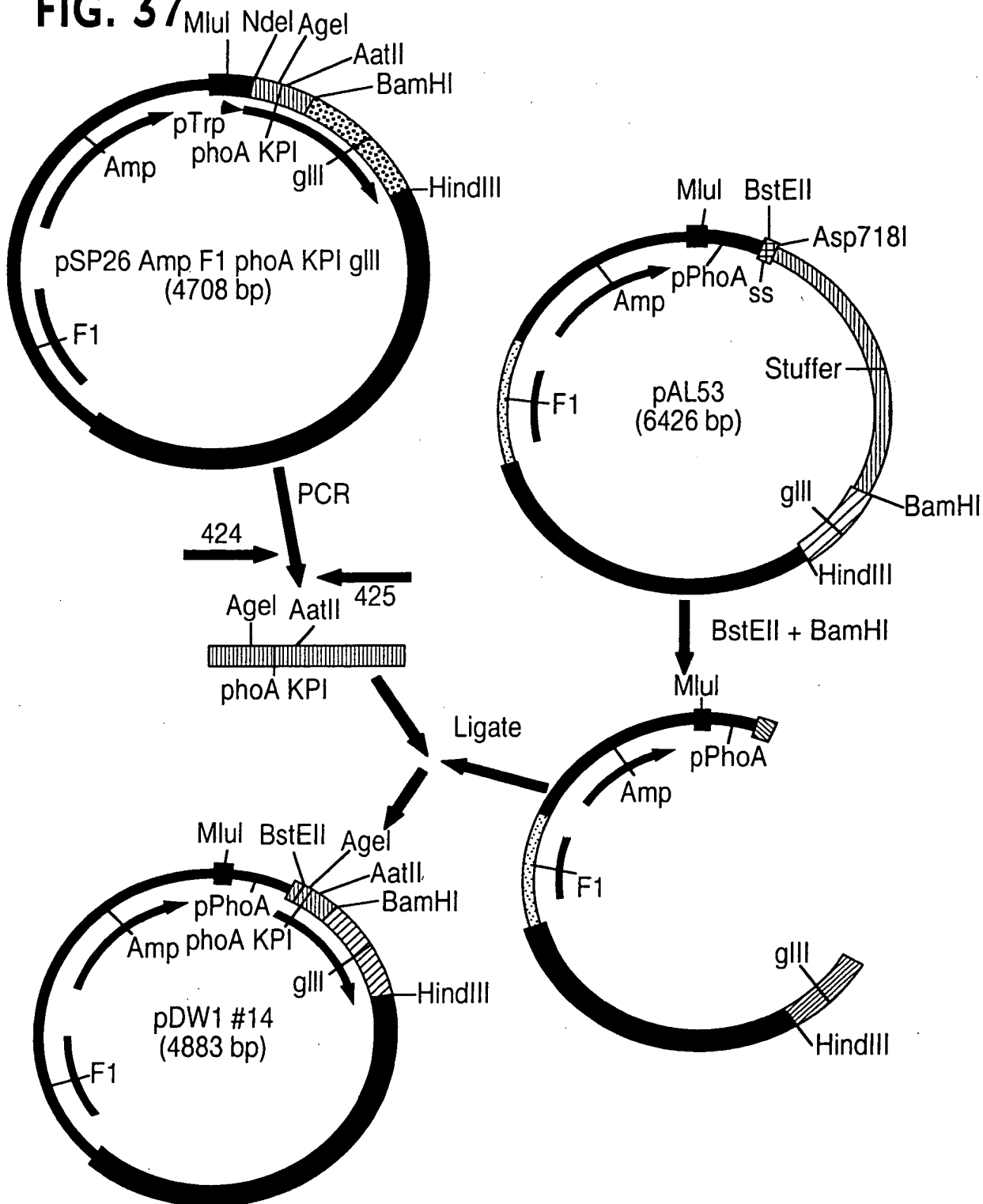
FIG. 35

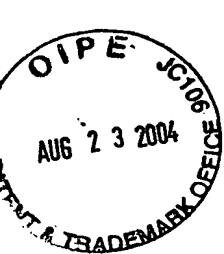


**FIG. 36**



**FIG. 37**





Title: PROTEASE INHIBITOR  
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FIG. 38

phoA signal →

BstEII

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA  
▶ Val Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55) →

Agel

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG  
▶ Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Met Ile Ser Arg Trp

AatII

TAC TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC  
▶ Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

BamHI

gIII →

CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT  
▶ Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser

GGT TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA  
▶ Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu

AAT GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT  
▶ Asn Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr

GAT TAC GGT GCT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT  
▶ Asp Tyr Gly Ala Ala Ile Asp Gly Phe Ile Gly Asp Val Ser Gly Leu Ala Asn Gly Asn

GGT GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT  
▶ Gly Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp

AAT TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA  
▶ Asn Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr Leu Pro Ser Leu Pro Gln Ser Val Glu

TGT CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA  
▶ Cys Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys

ATA AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA  
▶ Ile Asn Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val

TTT TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA  
▶ Phe Ser Thr Phe Ala Asn Ile Leu Arg Asn Lys Glu Ser • •

**FIG. 39**

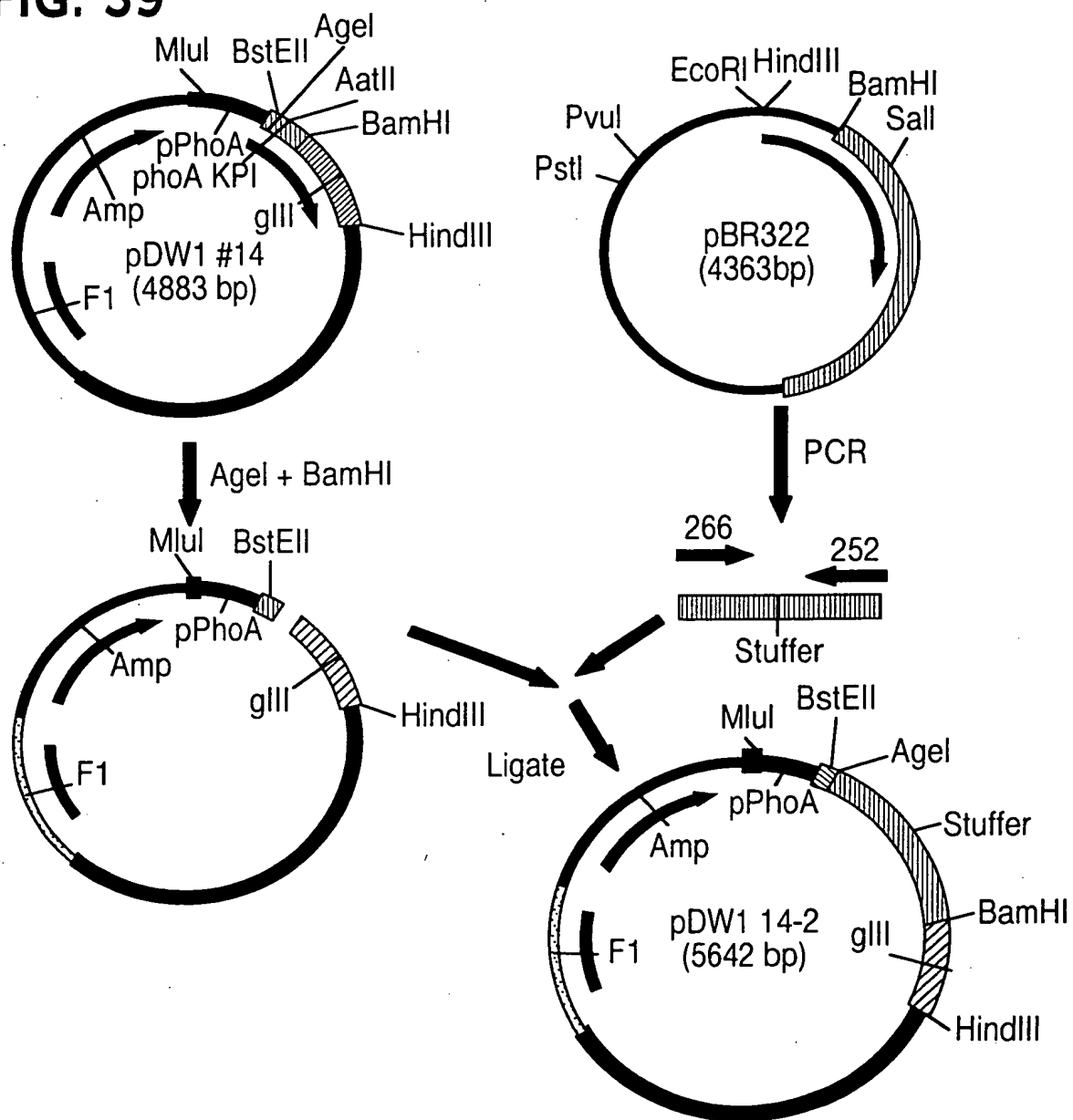
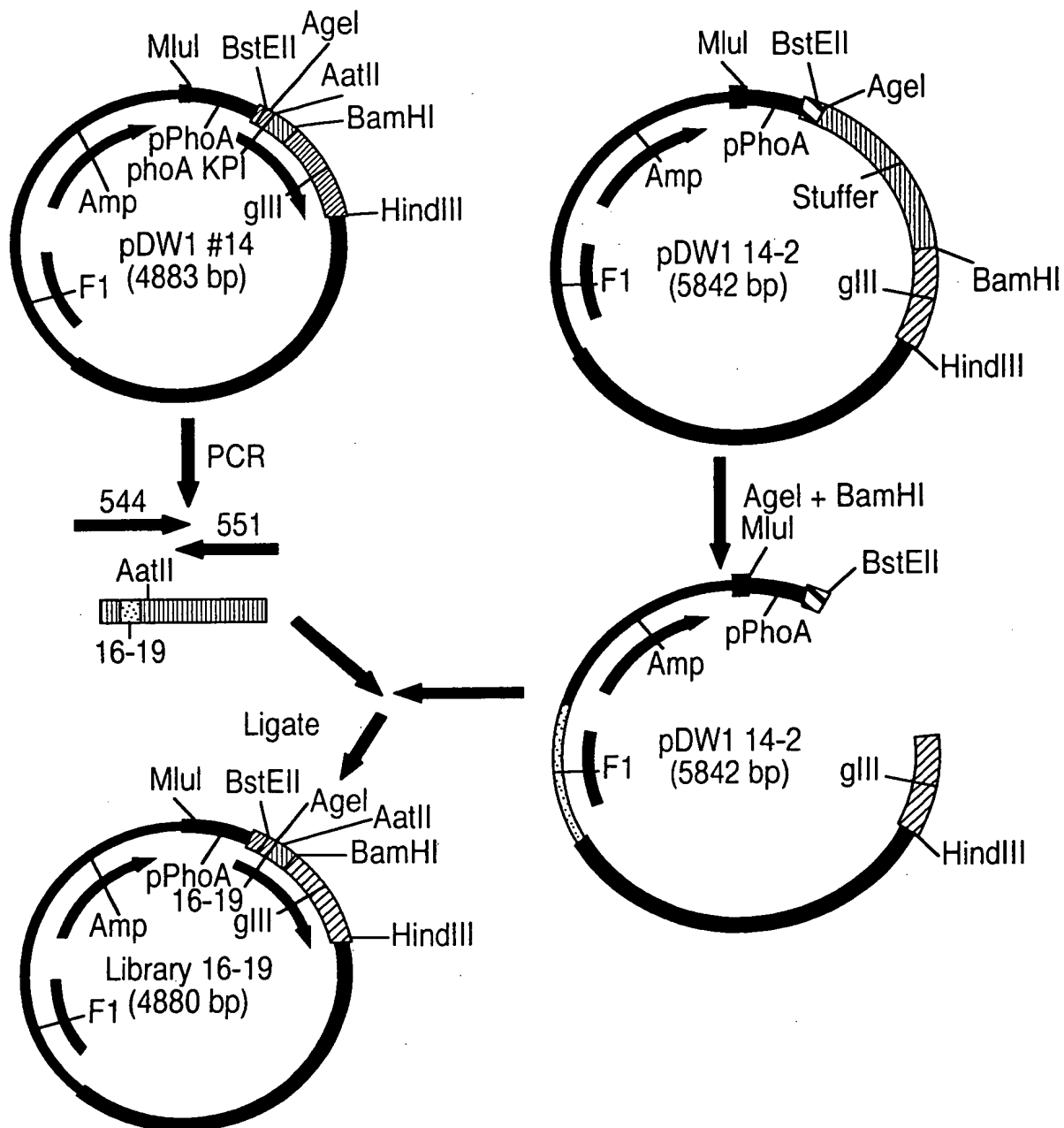
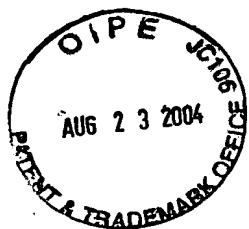


FIG. 40





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FIG. 41

phoA signal →

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA  
▶ Val Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

BstEII

KPI (1-55; 16 - 19) → Agel 16 - 19

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT NNS NNS NNS NNS TGG TAC  
▶ Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg --- --- --- --- Trp Tyr

AatII

TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT  
▶ Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg

BamHI gIII

AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT GGT  
▶ Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser Gly

TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA AAT  
▶ Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu Asn

GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT GAT  
▶ Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr Asp

TAC GGT GCT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT GGT  
▶ Tyr Gly Ala Ala Ile Asp Gly Phe Ile Gly Asp Val Ser Gly Leu Ala Asn Gly Asn Gly

gIII

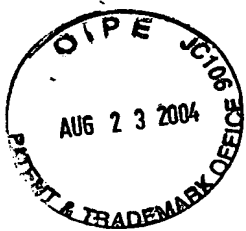
GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT AAT  
▶ Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp Asn

TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA TGT  
▶ Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr Leu Pro Ser Leu Pro Gln Ser Val Glu Cys

CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA ATA  
▶ Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys Ile

AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA TTT  
▶ Asn Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val Phe

TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA  
▶ Ser Thr Phe Ala Asn Ile Leu Arg Asn Lys Glu Ser • •



## FIG. 42

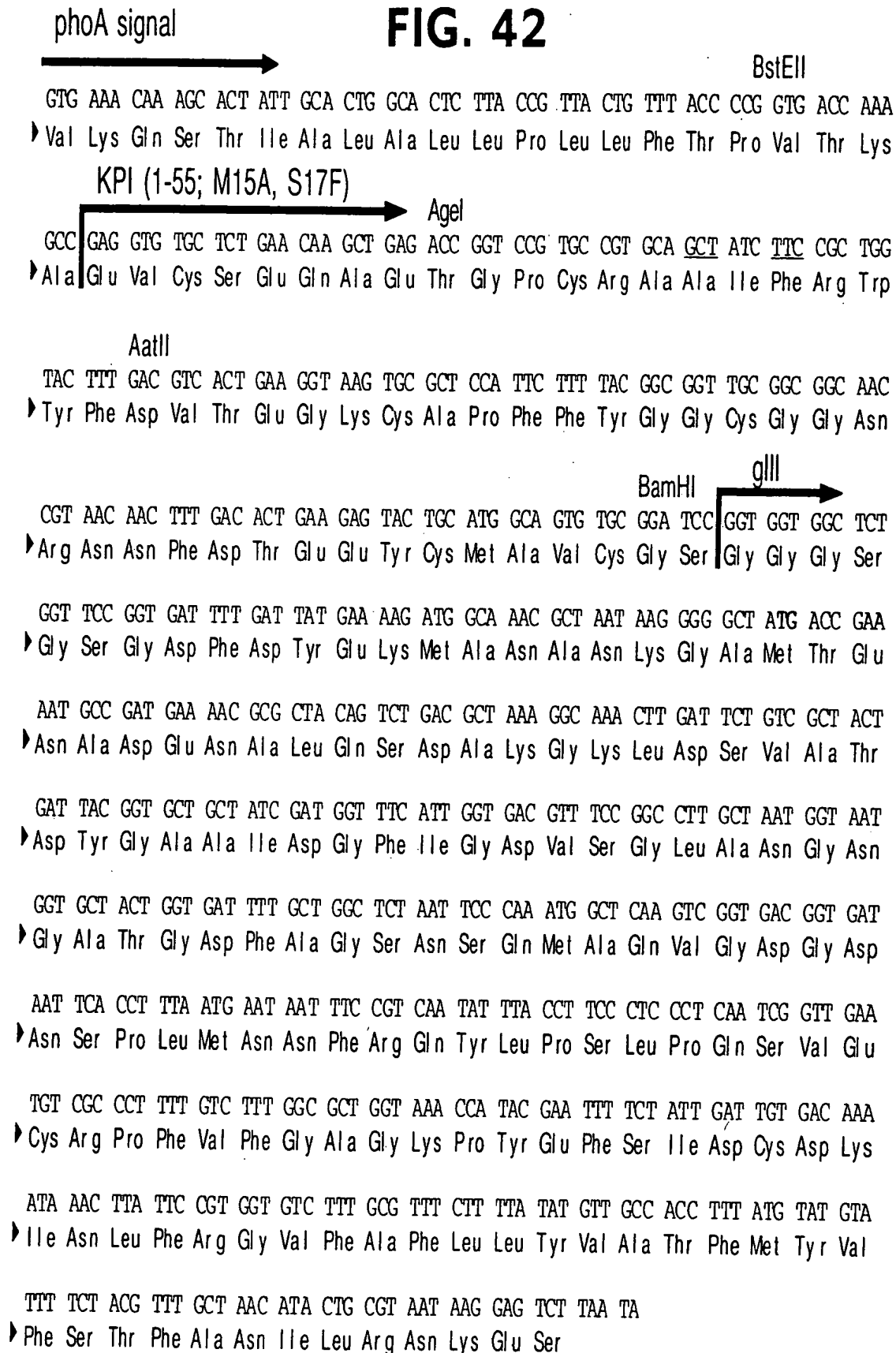
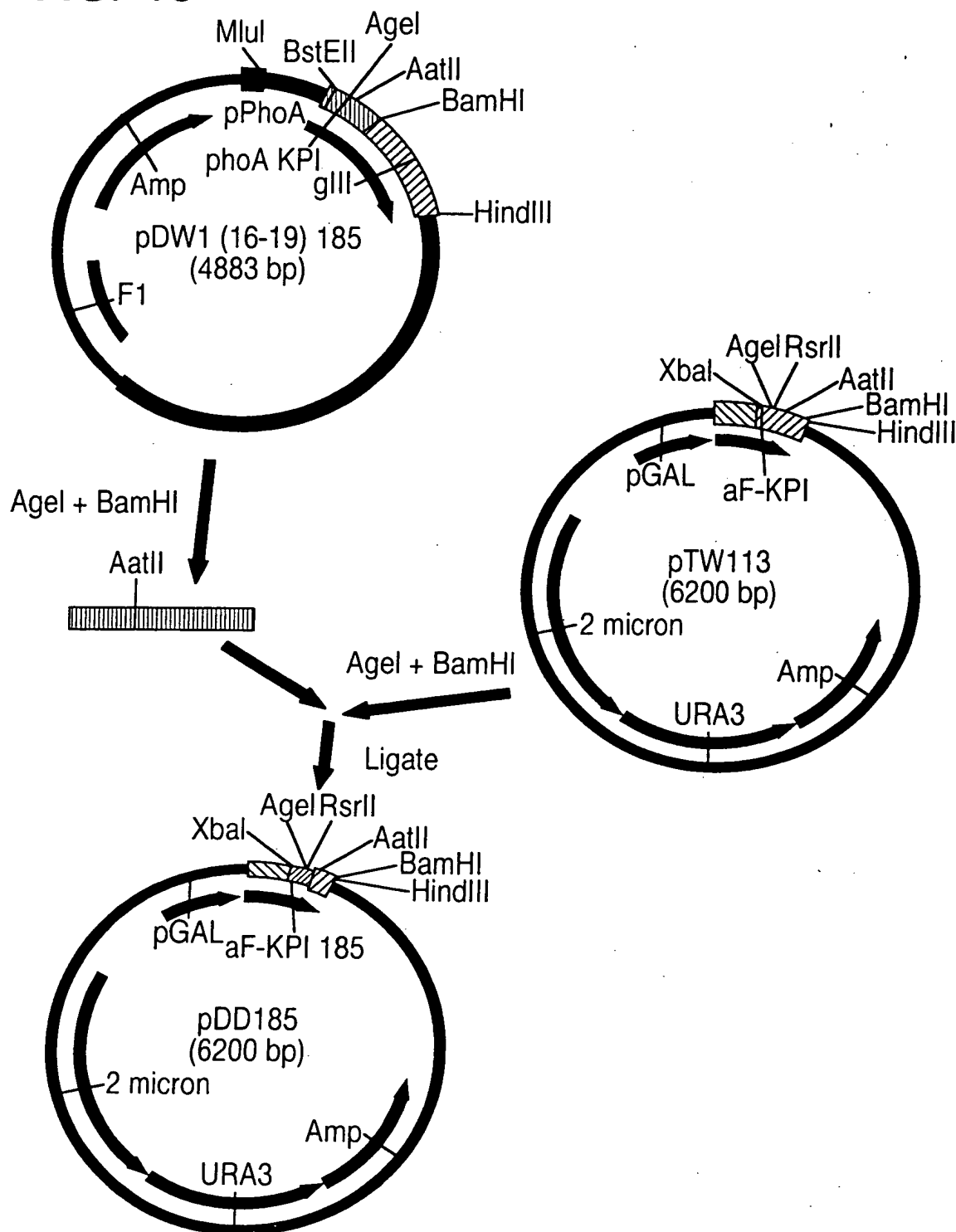




FIG. 43





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pDD185

## FIG. 44

$\alpha$ -factor



ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT  
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

► Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC  
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

► Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC  
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

► Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA  
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT

► Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

KPI(-4-57; M15A, S17F)

XbaI



GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA  
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT

► Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA  
CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT

► Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC  
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

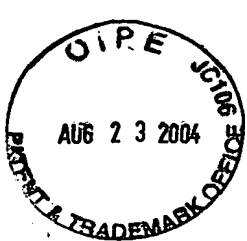
► Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T  
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

► Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile



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## FIG. 45

Plasma kallikrein inhibition by KPI (-4-57) variants

<u>Variant</u>	<u>Substitution</u>			<u>K<sub>i</sub>(nM)</u>
	15	16	17	
TW113				45.00
DD185			F	0.39
TW6165	A		W	0.65
TW6166	A		Y	0.40
TW6175	A		F	0.50
BG028	L		Y	1.10
TW6183	L		F	1.20
TW6184		H	Y	0.91
TW6185		H	W	1.30
TW6173	A	H		1.00
TW6174	L	H		0.90



FIG. 46A

Variant	Sequence	Inhibition Ki (nM)			
		kallikrein	Plasmin	XIIa	Xa
Aprotinin	RPDFCLEPPYTGPCAKARIIRYFYNAKAGLQTFVYGGCRAKRNNFASABDCRTCGGA	20.00	0.23	5000.0	
Aprotinin R15, S42	DFCLEPPYTGPCAKARIIRYFYNAKAGLQTFVYGGCRAKSNNFKSAEDCHRTCGGA	0.91	0.17	3983.0	
KPI (-4-57)	EVRVVCSEQAETGPCRAHISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	45.00	34.00	3718.0	161.0
TW6167	EVRVVCSEQAETGPCRAHISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	61.00		3641.0	288.0
BG031	EVRVVCSEQAETGPCRAHISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	34.00		498.0	
BG032	EVRVVCSEQAETGPCRAHISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	49.00		731.0	
TW101	EVCSEQAETGPCRAHISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	2000.00	11.50		
TW6208	EVRVVCSEQAETGPCRGRHISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI			369.0	
TW106	EVCSEQAETGPCRARISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	560.00	3.70		
DD108	EVRVVCSEQAETGPCRAAISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	1.70	11.20	1600.0	123.0
DD109	EVRVVCSEQAETGPCRAISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	9.50		1681.0	421.0
DD110	EVRVVCSEQAETGPCRALISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	2.10		624.0	55.0
DD111	EVRVVCSEQAETGPCRASISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	5.60			
DD112	EVRVVCSEQAETGPCRAVISRWYFDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	6.80		998.0	
TW6179	EVRVVCSEQAETGPCRAGISRWFVDVTEGKCAPFFYGGCGGHRNNFDTEEYCHAVCGSAI	78.00		368.0	



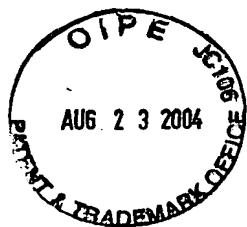
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Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 46B

TW6163	EVVREVCSEQAETGPCRAMHSRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	4.70	103.58	4532.0	457.0
TW6172	EVVREVCSEQAETGPCRAMASRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	315.00			1463.0
TW6180	EVVREVCSEQAETGPCRAMFSRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	70.00		885.0	39.0
TW6181	EVVREVCSEQAETGPCRAMKSRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	150.00		1514.0	
BG001	EVVREVCSEQAETGPCRAMLSRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	38.00	10.00	489.0	204.0
TW116	EVCSEQAETGPCRAMIIRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	145.00	89.00		806.0
DD102	EVVREVCSEQAETGPCRAMIPRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	16.00		315.0	
DD103	EVVREVCSEQAETGPCRAMIFRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	17.00		2128.0	110.0
DD104	EVVREVCSEQAETGPCRAMIYRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	15.00		237.0	345.0
DD105	EVVREVCSEQAETGPCRAMIWRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	18.00		198.0	320.0
TW6168	EVVREVCSEQAETGPCRAMILRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	25.80		3521.0	395.0
TW6182	EVVREVCSEQAETGPCRAMIHRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	36.00		732.0	
TW6194	EVVREVCSEQAETGPCRAMIERWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	70.83			
TW6210	EVVREVCSEQAETGPCRAMIQRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	54.00		277.0	
CL006	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI	110.20		89600.0	133.0
BG012	EVVREVCSEQAETGPCRAMISTWYFDVTEGKCAPFFYGGCGNRNPNFTTEBYCHAVCGSAI			40.0	116.0



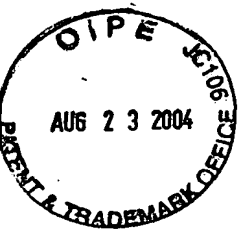
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PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 46C

TW6209	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	81.00	45.90	184.0	613.0
TW6211	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	184.00		402.0	
DD128	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	44.00			37.0
TW6142	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	18.00	18.00	7972.0	225.0
AL301	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	216.00		1557.0	
AL302	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	39.00			316.0
TW6147	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	35.00		1090.0	179.0
TW6138	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	18.00		921.0	309.0
TW6154	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	11.00		915.0	39.0
TW6155	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	11.00			27.0
TW6140	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	35.00		475.0	
TW6156	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI				
TW6141	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	42.00			
TW118	EVCQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	6.00	24.00	13009.0	68.0
DD100	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	15.00			
TW6157	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	40.00		511.0	168.0
TW6158	EVRVCSQAETGPCRAHISRHYFDVTEGKCAPFYGGCGNRNPNFTBYYCHAVCGSAI	29.00			



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FIG. 46D

TW6159	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	17.00			64.0
TW6161	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	7.50	18.00	1507.0	8.7
DD101	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	64.00		924.0	
TW6151	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	163.00		1162.0	954.0
TW6139	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	19.00	22.80	152.0	78.0
TW6153	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	11.20	21.30	65.0	36.0
TW122	EVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	32.00	27.00		581.0
TW6178	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	16.00		444.0	
TW6148	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	40.00			
TW124	EVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	64.00	48.00		
TW6149	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	54.00			
TW6173	EVVREVCSEQAETGPCRAHRSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	1.00	7.24	1432.0	
TW6174	EVVREVCSEQAETGPCRALHSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	0.90	6.89	2796.0	
BG002	EVVREVCSEQAETGPCRALLSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	0.98	19.00	403.0	60.0
DD129	EVVREVCSEQAETGPCRALFSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	3.60		1864.0	6.0
DD185	EVVREVCSEQAETGPCRAAIFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	0.39	8.71	150.0	196.0

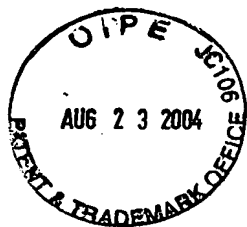


FIG. 46E

TW6165	EVRVVCSEQAETGPCRAAIIHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	0.65	16.40	206.0	
TW6166	EVRVVCSEQAETGPCRAAIIHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	0.4	10.10	73.0	
BG028	EVRVVCSEQAETGPCRALIIRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	1.10	12.10	93.8	
TW6169	EVRVVCSEQAETGPCRALIIRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	1.20		619.0	111.0
DD113	EVRVVCSEQAETGPCRALIIRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	0.85	12.80	293.0	74.0
TW6175	EVRVVCSEQAETGPCRALIIRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	0.50	7.46	35.0	56.0
TW6201	EVRVVCSEQAETGPCRAGIIRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	34.60		419.0	
TW6202	EVRVVCSEQAETGPCRAGIIRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	128.50		1237.0	
TW6203	EVRVVCSEQAETGPCRAGIIRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	31.20		5045.0	
TW6204	EVRVVCSEQAETGPCRAAIIHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI			147.0	87.0
TW6205	EVRVVCSEQAETGPCRALISAHYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI			195.0	29.0
DD114	EVRVVCSEQAETGPCRAAIIHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	0.70	7.77	224.0	
TW6190	EVRVVCSEQAETGPCRAAIIHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	0.83	52.20	589.0	1396.0
TW6183	EVRVVCSEQAETGPCRAHHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	1.20	11.68	12440.0	159.0
TW6184	EVRVVCSEQAETGPCRAHHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	0.91	11.96	14000.0	214.0
TW6185	EVRVVCSEQAETGPCRAHHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	1.30	18.60	388.0	473.0
BG003	EVRVVCSEQAETGPCRALIHRNYFDVTEGKCAPFFYGGCGGNRRNFDTEEYCHAVCGSAI	36.00		467.0	



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FIG. 46F

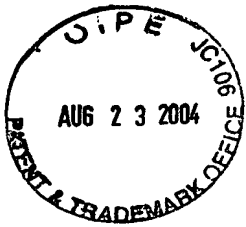
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TW6187	EVVREVCSEQAETGPCRAMIFRWYFDVTEGKCAPPFYGGCYGGRNNFDTBEYCHAVCGSAI	3.80	15.40	92.0	15.0
TW6188	EVVREVCSEQAETGPCRAMIYRWYFDVTEGKCAPPFYGGCYGGRNNFDTBEYCHAVCGSAI	4.00		419.0	24.0
TW6189	EVVREVCSEQAETGPCRAMIWRWYFDVTEGKCAPPFYGGCYGGRNNFDTBEYCHAVCGSAI	4.00			34.0
TW6170	EVVREVCSEQAETGPCRALILRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	2.50			452.0
DD115	EVVREVCSEQAETGPCRGYITRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI			213.0	299.0
DD170	EVVREVCSEQAETGPCRALHNRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	0.99	18.00	550.0	
TW6176	EVVREVCSEQAETGPCRAAHFRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	3.50	118.00	56.0	
TW6177	EVVREVCSEQAETGPCRALHFRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	7.20	32.70	245.0	156.0
BG006	EVVREVCSEQAETGPCRAALFRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	0.30	12.10	80.0	
DD130	EVVREVCSEQAETGPCRALFTRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	5.50			9.5
DD131	EVVREVCSEQAETGPCRALFKRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	7.90	2.00	1385.0	3.3
DD132	EVVREVCSEQAETGPCRAFFRWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	112.00			16.8
DD120	EVVREVCSEQAETGPCRAAFSAWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	8.30			11.0
DD121	EVVREVCSEQAETGPCRALLSAWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	19.00			21.0
BG014	EVVREVCSEQAETGPCRALIHWYFDVTEGKCAPPFYGGCGGRNNFDTBEYCHAVCGSAI	9.20	18.70	18.0	



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FIG. 46G

DD122	EVVREVCSEQAETGPCRAALIPAWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	15.00			46.0
BG015	EVVREVCSEQAETGPCRAALIYHWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	6.00	12.20	19.4	597.0
BG020	EVVREVCSEQAETGPCRAAIHKWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	1.70		106.0	
BG022	EVVREVCSEQAETGPCRAALIYHWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	0.64	7.26	14.5	
BG023	EVVREVCSEQAETGPCRAALIQHWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	23.00		262.0	
BG024	EVVREVCSEQAETGPCRAALIYKWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	4.10	7.47	38.7	
BG027	EVVREVCSEQAETGPCRAALIQHWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	5.80		144.0	
DD116	EVVREVCSEQAETGPCRAALIPRWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	0.14		583.0	84.0
TW6191	EVVREVCSEQAETGPCRAALIPRWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	0.26		664.0	20.0
DD117	EVVREVCSEQAETGPCRAALIPRWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	0.11		1034.0	99.0
BG029	EVVREVCSEQAETGPCRAALIYHWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	3.20		7.9	
BG030	EVVREVCSEQAETGPCRAALIYHWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	4.60		26.1	
BG033	EVVREVCSEQAETGPCRAALIYHWYFDVTEGKCAPFFYGGCGNRNNFDTEEYCHAVCGSAI	0.75		5.6	



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FIG. 46H

BC034	EWREVCSEQAETGPCRAAIYHMYFDVTEGKCAPFFYGGCGNRNFFDTEEYCHAVCGSAI	0.47		18.5
BC040	EWREVCSEQAETGPCRALIYHMYFDVTEGKCAPFFYGGCGNRNFFDTEEYCHAVCGSAI	3.40		8.6
BC016	EWREVCSEQAETGPCRGAIQHMYFDVTEGKCAPFFYGGCGNRNFFDTEEYCHAVCGSAI	160.00		178.0
BC017	EWREVCSEQAETGPCRGAIIRHMYFDVTEGKCAPFFYGGCGNRNFFDTEEYCHAVCGSAI	180.00		200.0
BC021	EWREVCSEQAETGPCRGSIIRHMYFDVTEGKCAPFFYGGCGNRNFFDTEEYCHAVCGSAI	340.00		224.0
BC025	EWREVCSEQAETGPCRGILIYHMYFDVTEGKCAPFFYGGCGNRNFFDTEEYCHAVCGSAI	65.00		16.2
BC026	EWREVCSEQAETGPCRGAIYHMYFDVTEGKCAPFFYGGCGNRNFFDTEEYCHAVCGSAI	50.00		34.9
DD118	EWREVCSEQAETGPCRALHNRWYFDVTEGKCAPFFYGGCGNRNFFDTEEYCHAVCGSAI	0.53		
DD134	EWREVCSEQAETGPCRALFKRWYFDVTEGKCAPFFYGGCYGNRNNFFDTEEYCHAVCGSAI	1.10	1.05	15640.0 0.6
DD135	EWREVCSEQAETGPCRALFKRWYFDVTEGKCAPFFYGGCLGNRNNFFDTEEYCHAVCGSAI	1.30		7473.0 0.9
DD136	EWREVCSEQAETGPCRALFKRWYFDVTEGKCAPFFYGGCMGNRNNFFDTEEYCHAVCGSAI	1.10		1.8

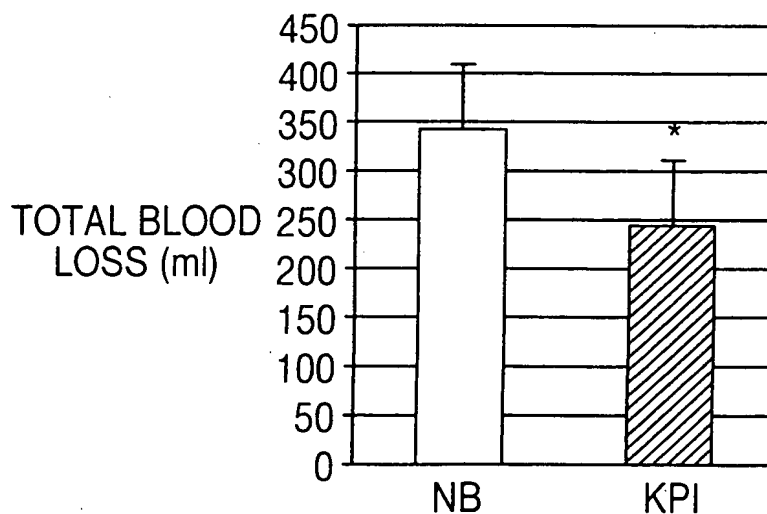


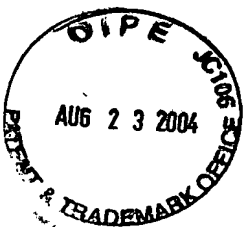
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## FIG. 47

### VOLUMES

NS	344.25	
KPI	245.75	
	KPI	NS
	298	366
	266	342
	354	294
	258	385
	168	288
	266	469
	172	338
	184	272
MEAN	245.75	344.25
STDEV	66.2414415	63.97488346
TTEST		0.009094999





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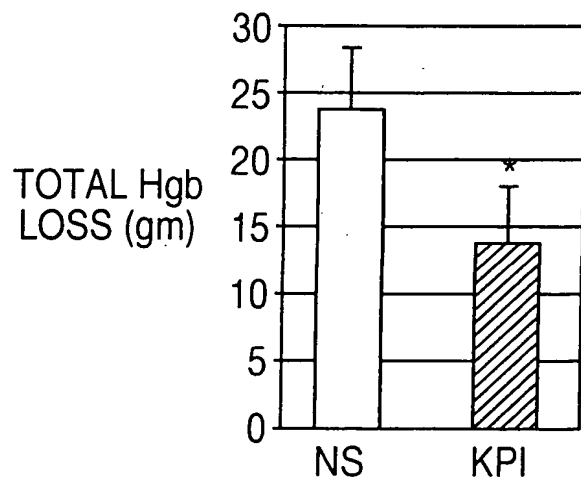
## FIG. 48

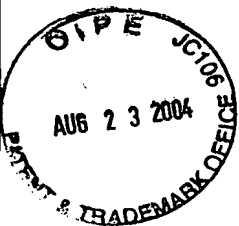
### HEMOGLOBIN

NS	23.61
KPI	13.59

	KPI	NS
	16.58	24.95
	15.19	24.87
	20.21	20.46
	8.99	27.59
	14.63	18.23
	15.31	31.59
	7.7	23.26
	10.14	17.96
MEAN	13.59375	23.61375
STDEV	4.261438	4.68761
TTEST	0.000536	





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## FIG. 49

PaO<sub>2</sub>

	Baseline PaO <sub>2</sub>		End CPB		Obs 60 min		Obs 180 min	
	KPI	NS	KPI	NS	KPI	NS	KPI	NS
	652.2	670.9	495.7	60.5	483.7	441.3	391.3	
	654	559.2	444.6	132.2	330.1	448.7	264.1	484.6
	596.2	622.9	170.2	93.8	415.4	85.1	416.5	81.3
	606.2	689.2	264.2	333.9	430.2	529.6	361.9	333.2
	633.1	665.1	567.2	341.7	613	568.3	90.8	546.6
	646.6	527	507.4	226.9	564.3	438.1	518.2	485.3
	563.2	461.7	547.1	89.1	501	42.6	494.2	45.6
	659.9	508	416.6	59.7	504.5	405.8	452	383.7
MEAN	626.425	588	426.625	167.225	480.275	369.938	371.1	344
STDEV	34.4692	85.5055	140.474	117.993	88.6187	196.523	150.277	186.22
TTEST	3	6	1	1	9	5	4	7
	p=	0.268	p=	0.0014	p=	0.17915	p=	0.76

N.S.

N.S.

# FIG. 50

## Summary of Data

### Total Volumes

	Total volume loss	Total Hgb Loss
KPI-1	298	16.58
KPI-2	266	15.19
KPI-3	354	20.21
KPI-4	258	8.99
KPI-5	168	14.63
KPI-6	266	15.31
KPI-7	172	7.7
KPI-8	184	10.14

MEAN	245.75	13.59
STDEV	66.24	4.26

NS-1A	366	24.95
NS-2	342	24.87
NS-3	294	20.46
NS-4	385	27.59
NS-5	288	18.23
NS-6	469	31.59
NS-7	338	23.26
NS-8	272	17.96

MEAN	344.25	23.61
STDEV	63.97	4.69

\*p = 0.009

\*p = 0.0005

### Serial Chest tube Hbg

	0-30min	30-60min	60-120min	120-180min
	3.7	4.3	8.6	6.2
	4.3	6.4	6.7	5.7
	4.1	4.4	7	7.1
	2.8	4	4.4	1.9
	6.3	6.5	7	6.7
	4.1	6.1	5.6	6.3
	3.1	4.6	5.4	4.4
	6.9	5.8	5.4	4.2

MEAN	4.41	5.26	6.26	5.3
STDEV	1.45	1.04	1.32	1.72

	7.7	8.6	6.1	5.4
	7.2	7.4	7.6	7.1
	5.4	7.5	7.5	6.5
	8.4	7.2	7.1	6.3
	7.5	7.2	5.2	5.6
	4	7	7.3	7.4
	7.5	7.7	5.8	4.2
	7.4	8.2	6	5.3

MEAN	6.89	7.6	6.58	6.1
STDEV	1.44	1.04	0.91	0.85

\*p = 0.004

\*p = 0.0002

NS

NS

